ANNUAL REPORT

OF

THE HOWE LABORATORY OF OPHTHALMOLOGY

HARVARD MEDICAL SCHOOL

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BOSTON, MASSACHUSETTS

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THE beginning of 1946 marked the termination of most of the government projects and again the Laboratory came into its own. The transition presented, as was expected, many problems, both of an organizational and a technical nature, and a report of the activities for 1946 is essentially a report of the attempt to make the most expeditious adjustment to the postwar conditions.

Organizational Activities

Bringing investigators with training in the basic sciences into intimate contact with clinical problems and clinical personnel has been a prime aim of the Howe Laboratory's organization and has, in some measure, set a pattern for laboratories elsewhere. After making a national survey of research facilities in ophthalmic and other fields, Dr. Kinsey has drawn up plans and made recommendations for the more wide spread adoption of research organizations similar to that of the Howe Laboratory whereby problems are conjointly studied by the clinician and by those whom Dr. Kinsey has termed the "medical scientists". This survey, to be published shortly, is especially timely in view of plans currently afoot for the reorganization of medical research on a nationwide basis.

Postgraduate teaching of basic sciences in ophthalmology had, before the War, become an increasingly important obligation of those few who, like the staff of the Howe Laboratory, profess to be specialists in this field. The end of the War resulted in a tremendous demand for training in the basic sciences in ophthalmology prior to the clinical residencies. As a result, two full time courses in the basic sciences occupying a total of five months, have been given during the past year to a total of sixty trainees. In the future it is planned to give one course of three months each year to approximately thirty men, the maximum which can be accommodated in the course laboratory work. In response to requests from those who are proposing to set up courses elsewhere, an outline has been prepared by Dr. Cogan, and will be published shortly, on the organization of basic science courses in ophthalmology. Since such courses, entailing extensive laboratory work, are new, there has been little precedent to follow and many of the teaching aids which

have been found most useful are being published separately e.g. an improved optical bench by Dr. Ludvigh, a model eye for slit-lamp microscopy by Dr. Grant, and a model for the demonstration of ocular movements by Dr. Cogan.

The illness and death of Dr. Theodore L. Terry in 1946 necessitated a change in the Pathology Department which he had so ably directed. Believing that there was mutual advantage in a close relationship between the pathology laboratory and the Howe Laboratory, Dr. Cogan accepted the appointment of Director of Ophthalmic Laboratories at the Massachusetts Eye and Ear Infirmary and for a time conducted the routine pathologic diagnoses. In this latter he was succeeded by Dr. Richard Pippitt who fortunately had joined the department before Dr. Terry's death. Both Dr. Cogan and Dr. Pippitt have depended heavily on the counsel of Dr. Frederick H. Verhoeff who graciously agreed to return as a consultant.

With the guidance of Miss Jeanette Loessl, the Howe Library has been a clearing house for the distribution of ophthalmological journals to leading ophthalmologists and institutions abroad. The journals have been and are continuing to be donated by physicians in this country who are willing to part with their current and wartime numbers and are directed, so far as possible, to European centers which need them the most. The response has been highly gratifying.

One of the problems facing the Howe Laborotory administration at the present time is how to accommodate the considerable number of qualified applicants who wish one to two years experience in an ophthalmic research laboratory before taking up academic positions elsewhere. Pending at the present time are applications from China, Europe and Canada as well as from this country. With rare exception, only those applicants are considered who are able to arrange for their own support; hence monetary support is not a problem of the Laboratory. The chief obstacle is space; further expansion of the Laboratory is not possible in the present quarters. It is hoped that additional space may be obtained, preferably at the Infirmary but elsewhere if necessary, to serve the important function of providing a place where future leaders in ophthalmology may obtain experience in research. It is certainly a vulnerable point in our present system of ophthalmic education that the majority of those

who head ophthalmic departments in this country have had little or no opportunity for first hand experience with ophthalmic research during their training and it is incumbent on the few ophthalmic research centers to make such facilities available so far as possible.

Research

Evidence has accumulated from studies both in the Howe Laboratory and elsewhere that the intraocular pressure is controlled by the secretion of some substance or substances into the aqueous humor. Were it possible to identify this substance and to regulate its secretion, one would have a basic understanding important not only for the physiologic processes in the normal eye but, conceivably, also for the control of glaucoma. To obtain fundamental data on the ocular secretory process, Dr. Kinsey is currently making an exhaustive study of ascorbic acid (vitamin C) metabolism in the eye. Ascorbic acid, being present in the normal aqueous humor in concentrations far in excess of that in the blood, obviously does not enter the eye merely by a process of diffusion. Dr. Kinsey's studies have been directed not only toward a determination of factors affecting the concentration of ascorbic acid in the aqueous humor with adequate blood levels but also the effect on the ocular secretory mechanism of altering the blood levels of ascorbic acid. Ascorbic acid appears to be necessary for secretion of aqueous humor since studies elsewhere have indicated that the formation of aqueous humor slows down or ceases in the absence of ascorbic acid; however, this function is not dependent on the antiscorbutic properties of the molecule since chemically related compounds (d-isoascorbic and d-gluco ascorbic acid) which are not antiscorbutic but which have the same oxidation-reduction potential, may be substituted and suffice for the secretion of aqueous humor. Further studies have, for the first time, demonstrated that with rising blood levels there is a maximum concentration of ascorbic acid which can be obtained in the aqueous humor of the normal adult eye, again showing that the blood and aqueous humor levels of ascorbic acid are not partitioned as a result of simple diffusion. No analogous maximum has been found for the anions (CI^-, SCN^-) investigated so far. Cations will

be similarly investigated as soon as the recently acquired Geiger counter and autoscaler are set up for the measurement of radioactive isotopes.

Stimulated by the disastrous consequences of sulphur dioxide burns of the eye which had occurred in a series of patients seen at the Infirmary, Dr. Grant has made an exhaustive study of the mode of action of this poison. Sulphur dioxide is a refrigerant, commonly used in household and industrial refrigerating systems, and its toxicity has heretofore been assumed to be due either to its freezing action or to the formation in situ of sulphuric acid. Dr. Grant found neither of these to be important factors. Sulphur dioxide maintained its toxic properties even when its freezing action was eliminated and, conversely, experimental freezing of the eye with some inert refrigerant had little effect compared with that of sulphur dioxide. Nor was the amount of sulphuric acid formed sufficient to account for its toxicity. Dr. Grant did find, however, that the peculiar property of sulphur dioxide which made it extraordinarily toxic was attributable to the lipoid solubility of the gas and its consequent ability to traverse the corneal epithelium rapidly; once in the stroma it formed sulphurous (not sulphuric) acid and as such denatured the enzymes and other corneal proteins. It is the only apparent instance of a weak acid becoming toxic because of the penetrability of one of its gaseous dissociation products.

Incidental to this study, a new and highly sensitive coloremetric method was devised for measuring sulphur dioxide in tissues and blood.

Biochemical studies are currently being conducted by Dr. Grant on methyl alcohol with the purpose of elucidating the deleterious effect of this substance on vision. In the course of this study a low temperature vacuum distillation apparatus has been developed which has proven useful in various analytical procedures on small samples of biological material. A description of this apparatus has been published. Also as part of the study of methyl alcohol, a method has been devised many times more sensitive than previous methods for measurement of formic acid, an oxidation product of methyl alcohol, in blood.

Preliminary investigation has also been made on the

ocular effects of methyl bromide, neutral cyanide, digitonin, hydroxylamine, a new silicone grease, and urea.

The extent to which visual acuity is affected by continuous rotary or horizontal movement of the test object is being currently investigated by Dr. Ludvigh. In view of the exhaustive studies that have been made of the visual acuity of stationary objects, it is curious that no previous studies have been made for moving objects. Its practical importance was emphasized during the War when it was necessary to design optical equipment for "tracking" airplanes, but it is also important for many civilian functions when viewing moving objects or, conversely, when, as in nystagmus, the eye instead of the object is moving. Aside from obtaining fundamental data on visual acuity during movement, the possibility will be explored that a provocative test may be developed using a moving target for the detection of incipient ocular motor disturbances.

Vascularization of the cornea is an important problem from a clinical point of view and an intriguing one from a physiologic point of view. While the causes of corneal vascularization are many and have been variously studied, the pathogenesis of the vascularizing process itself has not heretofore been elucidated. Dr. Cogan has made a study of the events occurring during vascularization of the rabbit cornea and has presented evidence indicating that the significant factor in the stimulus for neovasculogenesis is a decrease in tissue compactness.

A statistical survey of the results of various glaucoma operations was made by Dr. Albert N. Lemoine during his tenure as Fellow in Ophthalmic Research.

Under the joint aegis of the Howe Laboratory and Department of Bacteriology at the Harvard Medical School, Dr. Henry F. Allen has made a study of the effect of sodium iodide on the herpes simplex virus. Although reports elsewhere had suggested that sodium iodide was efficacious in the treatment of ulcers of the cornea caused by this virus, Dr. Allen was unable to demonstrate any significant effect of the agent on herpes simplex infections of the eyes of

rabbits and mice nor on the inoculum of chorioallantoic membrane cultures with this virus.

The possibility of using a spot light for projection campimetry is currently being explored by Dr. Biegel and Dr. Ludvigh. A pilot model apparatus has been set up in the Field Room adjacent to the Clinic and the results obtained by this method on patients is being compared with the results obtained by the orthodox procedures.

Other noteworthy activities of the Howe Laboratory to be published in detail elsewhere are the studies on the neurologic significance of lateral conjugate deviation of the eyes with forced closure of the lids by Dr. Cogan, the preparation of a bibliography covering ophthalmic biochemistry, pharmacology, and toxicology for the years 1944–1946 by Dr. Grant, the supervision of research on tunica fibroplasia lentis by Dr. Kinsey, the preparation of a text-book chapter on pediatric ophthalmology by Dr. Cogan, and the construction of a device permitting fundamental research in the field of light difference sensitivity by Dr. Ludvigh. Finally, the Howe Laboratory continues with mutual profit to serve in consultation for a wide variety of interests where ophthalmic research is involved and to participate in the presentation of papers and discussions at various meetings.

Support of the Laboratory

A major problem facing the Howe Laboratory is that of finances. Increased operating expenses (supplies, equipment, services and wages) is especially disconcerting for endowed institutions with fixed capital. The operating cost has practically doubled and, were outside funds not forthcoming, the Laboratory would naturally have to shrink accordingly. In view of the increasing importance of the Laboratory this would seem most unfortunate. Fortunately several agencies and individuals noted below have generously made supplementary additions to the Laboratory income. While this is chiefly in the form of project donation and does not provide a long term solution, it does enable the Laboratory to maintain its present staff and to continue its important work. It is to be hoped that in the future additional endowment may be obtained. The following have by their support made

possible much of the investigation noted in the foregoing report. To them, and to others who have contributed in less tangible ways, the Laboratory is profoundly grateful.

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Mr. Frank E. Goddard for general expenses.

Mrs. Francis I. Proctor for the cost of sending journals abroad.

DAVID G. COGAN, M.D.
Director

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